Clinical trial results:
A Multicenter, Multinational, Double-Blind, Placebo-Controlled, 2-Arm Study to Evaluate the Efficacy of Rotigotine on Parkinson's Disease-Associated Pain

Summary

EudraCT number	2012-002608-42
Trial protocol	DE GB HU SK
Global end of trial date	30 January 2014

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	25 April 2015

Trial information

Trial identification

Sponsor protocol code	PD0004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01744496
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES GmbH
Sponsor organisation address	Alfred-Nobel-Str. 10, Monheim, Germany, 40789
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of Rotigotine over placebo on improvement of Parkinson’s disease associated chronic pain in subjects with advanced-stage Parkinson’s disease experiencing Parkinson’s disease associated chronic pain.

Protection of trial subjects:

Close monitoring of subjects safety status, including checks of mental health e.g. by CSSR-S questionnaire.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	19 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Slovakia: 16
Worldwide total number of subjects	68
EEA total number of subjects	37

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	27
From 65 to 84 years	40
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Europe and USA. Recruitment was planned to continue until approximately 64 patients were randomized in the study. Subjects were randomized in a 1:1 ratio to either Rotigotine or Placebo. To achieve this, approximately 28 investigational sites were planned to participate in this hypothesis-generating pilot study.

Pre-assignment

Screening details:

The Participant Flow population refers to the Randomized Set (RS). The RS includes all subjects who were randomized.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo Transdermal PatchesPlacebo: Placebo patches matched the size of active patches 20 cm^2, 30 cm^2, or 40 cm^2 and contained Placebo. Application of Placebo patches started at the Baseline Visit. Placebo patches were administered once daily starting with the equivalent of 4 mg / 24 h. Doses were then up-titrated in weekly equivalents to 2 mg / 24 h until either optimal dose or maximum dose was reached. The maximum dose was the equivalent to 16 mg / 24 h. The duration of the Titration Period varied from 1 to 7 weeks. The Maintenance Period lasted 12 weeks ± 5 days. During the De-Escalation Period, the dose of Placebo was decreased by the equivalent to 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Placebo patches matched the size of active patches 20 cm^2, 30 cm^2, or 40 cm^2 and contained Placebo. Application of Placebo patches started at the Baseline Visit. Placebo patches were administered once daily starting with the equivalent of 4 mg / 24 h. Doses were then up-titrated in weekly equivalents to 2 mg / 24 h until either optimal dose or maximum dose was reached. The maximum dose was the equivalent to 16 mg / 24 h. The duration of the Titration Period varied from 1 to 7 weeks. The Maintenance Period lasted 12 weeks ± 5 days. During the De-Escalation Period, the dose of Placebo was decreased by the equivalent to 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Arm title	Rotigotine

Arm description:

Rotigotine Transdermal PatchesRotigotine: Patches contained 4 mg / 24 h (20 cm^2), 6 mg/ 24 h (30 cm^2), or 8 mg /24 h (40 cm^2) of Rotigotine. Application of study medication started at the Baseline Visit. Rotigotine was administered once daily starting at 4 mg / 24 h. Doses were then up-titrated in weekly increments of 2 mg / 24 h until optimal or maximum dose (16 mg / 24 h) was reached and the Maintenance Period could be started. The duration of the Titration Period varied from 1 to 7 weeks ± 3 days. The Maintenance Period lasted 12 weeks ± 5 days. Thereafter, during the De-Escalation Period, the dose of study medication was decreased by 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Arm type	Experimental
Investigational medicinal product name	Rotigotine
Investigational medicinal product code	
Other name	Neupro
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Patches contained 4 mg / 24 h (20 cm^2), 6 mg/ 24 h (30 cm^2), or 8 mg /24 h (40 cm^2) of Rotigotine. Application of study medication started at the Baseline Visit. Rotigotine was administered once daily starting at 4 mg / 24 h. Doses were then up-titrated in weekly increments of 2 mg / 24 h until optimal or maximum dose (16 mg / 24 h) was reached and the Maintenance Period could be started. The duration of the Titration Period varied from 1 to 7 weeks ± 3 days. The Maintenance Period lasted 12 weeks ± 5 days. Thereafter, during the De-Escalation Period, the dose of study medication was decreased by 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Number of subjects in period 1	Placebo	Rotigotine
Started	33	35
Maintenance Period	31	33
Titration Period	33	35
Completed	27	29
Not completed	6	6
Consent withdrawn by subject	1	1
Personal reasons	-	1
AE, non-serious non-fatal	2	3
Subject left town	1	-
SAE, non-fatal	1	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Placebo Transdermal PatchesPlacebo: Placebo patches matched the size of active patches 20 cm^2, 30 cm^2, or 40 cm^2 and contained Placebo. Application of Placebo patches started at the Baseline Visit. Placebo patches were administered once daily starting with the equivalent of 4 mg / 24 h. Doses were then up-titrated in weekly equivalents to 2 mg / 24 h until either optimal dose or maximum dose was reached. The maximum dose was the equivalent to 16 mg / 24 h. The duration of the Titration Period varied from 1 to 7 weeks. The Maintenance Period lasted 12 weeks ± 5 days. During the De-Escalation Period, the dose of Placebo was decreased by the equivalent to 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Reporting group title	Rotigotine

Reporting group description:

Rotigotine Transdermal PatchesRotigotine: Patches contained 4 mg / 24 h (20 cm^2), 6 mg/ 24 h (30 cm^2), or 8 mg /24 h (40 cm^2) of Rotigotine. Application of study medication started at the Baseline Visit. Rotigotine was administered once daily starting at 4 mg / 24 h. Doses were then up-titrated in weekly increments of 2 mg / 24 h until optimal or maximum dose (16 mg / 24 h) was reached and the Maintenance Period could be started. The duration of the Titration Period varied from 1 to 7 weeks ± 3 days. The Maintenance Period lasted 12 weeks ± 5 days. Thereafter, during the De-Escalation Period, the dose of study medication was decreased by 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Reporting group values	Placebo	Rotigotine	Total
Number of subjects	33	35	68
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	12	27
From 65-84 years	17	23	40
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	65.3	66.5	
standard deviation	± 13.8	± 11.9	-
Gender categorical Units: Subjects			
Male	17	19	36
Female	16	16	32
Race/Ethnicity, Customized Units: Subjects			
American Indian / Alaskan native	0	0	0
Asian	1	0	1
Black	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0

White	32	35	67
Other / mixed	0	0	0

Weight			
Units: kilograms			
arithmetic mean	80.15	77.8	
standard deviation	± 20	± 13.71	-
Height			
Units: centimeters			
arithmetic mean	167.17	168.63	
standard deviation	± 9.92	± 9.87	-
Body Mass Index (BMI)			
Units: kilogram per squaremeter			
arithmetic mean	28.54	27.419	
standard deviation	± 6.211	± 4.743	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo Transdermal PatchesPlacebo: Placebo patches matched the size of active patches 20 cm^2, 30 cm^2, or 40 cm^2 and contained Placebo. Application of Placebo patches started at the Baseline Visit. Placebo patches were administered once daily starting with the equivalent of 4 mg / 24 h. Doses were then up-titrated in weekly equivalents to 2 mg / 24 h until either optimal dose or maximum dose was reached. The maximum dose was the equivalent to 16 mg / 24 h. The duration of the Titration Period varied from 1 to 7 weeks. The Maintenance Period lasted 12 weeks ± 5 days. During the De-Escalation Period, the dose of Placebo was decreased by the equivalent to 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Reporting group title	Rotigotine

Reporting group description:

Rotigotine Transdermal PatchesRotigotine: Patches contained 4 mg / 24 h (20 cm^2), 6 mg/ 24 h (30 cm^2), or 8 mg /24 h (40 cm^2) of Rotigotine. Application of study medication started at the Baseline Visit. Rotigotine was administered once daily starting at 4 mg / 24 h. Doses were then up-titrated in weekly increments of 2 mg / 24 h until optimal or maximum dose (16 mg / 24 h) was reached and the Maintenance Period could be started. The duration of the Titration Period varied from 1 to 7 weeks ± 3 days. The Maintenance Period lasted 12 weeks ± 5 days. Thereafter, during the De-Escalation Period, the dose of study medication was decreased by 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Subject analysis set title	FAS (Placebo treated subjects)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set is a subset of the Safety Set and includes all subjects who were randomized, received at least 1 dose of study medication, and had a valid primary efficacy Baseline measurement and at least 1 valid post-Baseline Maintenance or valid withdrawal primary efficacy measurement.

Subject analysis set title	FAS (Rotigotine treated subjects)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set is a subset of the Safety Set and includes all subjects who were randomized, received at least 1 dose of study medication, and had a valid primary efficacy Baseline measurement and at least 1 valid post-Baseline Maintenance or valid withdrawal primary efficacy measurement.

Primary: Change from Baseline to the End of the Maintenance Period in pain severity assessed using an 11-point Likert Pain Scale

End point title	Change from Baseline to the End of the Maintenance Period in pain severity assessed using an 11-point Likert Pain Scale

End point description:

An 11-Point Likert Scale was used to assess patients' average daily pain. The subject rated his/her average pain from 0 (no pain) to 10 (worst pain ever experienced).
The average pain experienced in the last 7 days was calculated by the mean of the daily Likert Pain Scores within the 7 days prior to the respective visit (ie, Likert Pain Scores with a date of assessment before the date of visit and on or after the date of visit – 7 days). A negative value indicates an improvement.

End point type	Primary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period (Maintenance Period lasts 12 weeks ± 5 days after an up to 7 weeks Titration Period)

End point values	Placebo	Rotigotine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[1]	30[2]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-2.2 (± 2.78)	-2.8 (± 1.84)		

Notes:

[1] - Full Analysis Set (FAS)

[2] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to the End of Treatment containing treatment and region as factors and Baseline value as a covariate.

Comparison groups	Placebo v Rotigotine
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.55

Secondary: Percentage of Responders at the End of the Maintenance Period

End point title	Percentage of Responders at the End of the Maintenance Period

End point description:

Responders are defined as patients experiencing a 2-Point or more Reduction on an 11-Point Likert Pain Scale from Baseline to the End of the Maintenance Period. An 11-Point Likert Scale was used to assess patients' average daily pain. The patient rated his/her average pain from 0 (no pain) to 10 (worst pain ever experienced).

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period (Maintenance Period lasts 12 weeks ± 5 days after up to 7 weeks Titration Period)

End point values	Placebo	Rotigotine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[3]	30[4]		
Units: percentage of responders				
number (not applicable)				
percentage of responders	46.7	60		

Notes:

[3] - Full Analysis Set (FAS)

[4] - Full Analysis Set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the End of the Maintenance Period in the sum score of the 8-Item Parkinson's Disease Questionnaire (PDQ-8)

End point title	Change from Baseline to the End of the Maintenance Period in the sum score of the 8-Item Parkinson's Disease Questionnaire (PDQ-8)

End point description:

The 8-Item Parkinson's Disease Questionnaire (PDQ-8) (Peto et al, 1998) is a self-administered questionnaire that provides a reliable measure of overall health status. The PDQ-8 contains 8 items of daily living, with 1 item selected from each of the following 8 scales: mobility, Activities of Daily Living (ADL), emotional well being, stigma, social support, cognitions, communication, and bodily discomfort. The total PDQ-8 score is the sum of all the individual items converted to a summary index score between 0 and 100, with lower scores indicating better health. A negative value indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period (Maintenance Period lasts 12 weeks ± 5 days after up to 7 weeks Titration Period)

End point values	Placebo	Rotigotine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[5]	30[6]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-3.77 (± 13.93)	-12.4 (± 19.25)		

Notes:

[5] - Full Analysis Set (FAS)

[6] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to the End of Treatment containing treatment and region as factors and Baseline value as a covariate.

Comparison groups	Placebo v Rotigotine

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-8.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.56
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	3.77

Secondary: Change from Baseline to the End of the Maintenance Period in the 7-Item Depression subscore of the Hospital Anxiety and Depression Scale (HADS)

End point title	Change from Baseline to the End of the Maintenance Period in the 7-Item Depression subscore of the Hospital Anxiety and Depression Scale (HADS)

End point description:

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) is a 14-item self-assessment scale for detecting states of depression and anxiety in the setting of a hospital medical outpatient clinic. It comprises a 7-item anxiety subscale and a 7-item depressive subscale that are also measures of severity of the emotional disorder. The 14 items are scored between 0 and 3. The 7-item depression subscore and 7-item anxiety subscore were calculated as the sum of the 7 corresponding individual scores. A negative value indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period (Maintenance Period lasts 12 weeks ± 5 days after up to 7 weeks Titration Period)

End point values	Placebo	Rotigotine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[7]	28[8]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-1.7 (± 4.3)	-1.9 (± 4.1)		

Notes:

[7] - Full Analysis Set (FAS)

[8] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to the End of Treatment containing treatment and region as factors and Baseline value as a covariate.

Comparison groups	Placebo v Rotigotine

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.76
upper limit	0.73
Variability estimate	Standard error of the mean
Dispersion value	0.87

Secondary: Change from Baseline to the End of the Maintenance Period in the 7-Item Anxiety subscore of the Hospital Anxiety and Depression Scale (HADS)

End point title	Change from Baseline to the End of the Maintenance Period in the 7-Item Anxiety subscore of the Hospital Anxiety and Depression Scale (HADS)

End point description:

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) is a 14-item self-assessment scale for detecting states of depression and anxiety in the setting of a hospital medical outpatient clinic. It comprises a 7-item anxiety subscale and a 7-item depressive subscale that are also measures of severity of the emotional disorder. The 14 items are scored between 0 and 3. The 7-item depression subscore and 7-item anxiety subscore were calculated as the sum of the 7 corresponding individual scores. A negative value indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period (Maintenance Period lasts 12 weeks ± 5 days after up to 7 weeks Titration Period)

End point values	Placebo	Rotigotine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[9]	28[10]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-1 (± 3.2)	-1.8 (± 3.7)		

Notes:

[9] - Full Analysis Set (FAS)

[10] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to the End of Treatment containing treatment and region as factors and Baseline value as a covariate.

Comparison groups	Placebo v Rotigotine

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.371
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.64

Secondary: Change from Baseline to the End of the Maintenance Period in the combined score of the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (Activities of Daily Living [ADL] subscale) and III (motor subscale)

End point title	Change from Baseline to the End of the Maintenance Period in the combined score of the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (Activities of Daily Living [ADL] subscale) and III (motor subscale)

End point description:

Part II of the Unified Parkinson's Disease Rating Scale (UPDRS) assesses the subject's activities of daily living. Part III assesses motor function. The UPDRS is completed by questioning the subject about his/her general state in conjunction with any observations made by the investigator (or designee) since the previous visit. Part II is subject-rated and Part III is physician-rated. The UPDRS Part II (Activities of Daily Living) consists of 13 items scored between 0 and 4. The sum score was calculated as the sum of these 13 individual scores. The UPDRS Part III (motor subscale) consists of 27 items and sub items scored between 0 and 4. The sum score was calculated as sum of these 27 individual scores. The sum score of UPDRS Parts II and III is the sum of the corresponding single sum scores. A negative value indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period (Maintenance Period lasts 12 weeks ± 5 days after up to 7 weeks Titration Period)

End point values	Placebo	Rotigotine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[11]	30[12]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-5.1 (± 11.7)	-8.3 (± 11.2)		

Notes:

[11] - Full Analysis Set (FAS)

[12] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

ANCOVA model for the change from Baseline to the End of Treatment containing treatment and region as factors and Baseline value as a covariate.

Comparison groups	Placebo v Rotigotine
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.346
Method	ANCOVA
Parameter estimate	Least Square Mean
Point estimate	-2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.76
upper limit	3.13
Variability estimate	Standard error of the mean
Dispersion value	2.97

Secondary: Change from Baseline to the End of the Maintenance Period in the 7 domain scores of Classification of Pain in Parkinson's Disease

End point title	Change from Baseline to the End of the Maintenance Period in the 7 domain scores of Classification of Pain in Parkinson's Disease

End point description:

The classification of pain in Parkinson’s disease scale classifies pain in the following domains: musculoskeletal pain (item 1), chronic pain (items 2 and 3), fluctuation related pain (items 4, 5 and 6), nocturnal pain (items 7 and 8), oro-facial pain (items 9, 10 and 11), discoloration; edema/swelling (items 12 and 13), and radicular pain (item 14). Severity of the pain is measured on a scale from none (0) to severe (3) and frequency is measured on a scale from never (0) to very frequent (4).
A score of a single item was calculated by multiplying severity with frequency. A domain score was calculated as the sum of every individual score related to the respective domain. A negative value indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) until End of the Maintenance Period (Maintenance Period lasts 12 weeks ± 5 days after up to 7 weeks Titration Period)

End point values	Placebo	Rotigotine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[13]	30[14]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Musculoskeletal Pain	-1.4 (± 3.6)	-1.5 (± 4.2)		
Chronic Pain	-3.1 (± 5.6)	-0.7 (± 2.9)		
Fluctuation-Related Pain	-2.2 (± 4.6)	-4.2 (± 6.8)		
Nocturnal Pain	-2.9 (± 6.1)	-2.4 (± 5.3)		
Oro-Facial Pain	-0.4 (± 2.5)	-0.6 (± 2.3)		

Discoloration; Edema/Swelling Radicular Pain	-1.8 (± 4.9) -1.3 (± 3.8)	-1.7 (± 3.4) -1.1 (± 3.7)		

Notes:

[13] - Full Analysis Set (FAS)

[14] - Full Analysis Set (FAS)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events were reported from Baseline up to the Safety Follow-up Visit (approximately during 25 weeks).

Adverse event reporting additional description:

Adverse Events (AEs) refer to the Safety Set (SS). The SS includes all randomized subjects who received at least 1 dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo Transdermal Patches

Placebo: Placebo patches matched the size of active patches 20 cm^2, 30 cm^2, or 40 cm^2 and contained Placebo. Application of Placebo patches started at the Baseline Visit. Placebo patches were administered once daily starting with the equivalent of 4 mg / 24 h. Doses were then up-titrated in weekly equivalents to 2 mg / 24 h until either optimal dose or maximum dose was reached. The maximum dose was the equivalent to 16 mg / 24 h. The duration of the Titration Period varied from 1 to 7 weeks. The Maintenance Period lasted 12 weeks ± 5 days. During the De-Escalation Period, the dose of Placebo was decreased by the equivalent to 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Reporting group title	Rotigotine

Reporting group description:

Rotigotine Transdermal Patches

Rotigotine: Patches contained 4 mg / 24 h (20 cm^2), 6 mg/ 24 h (30 cm^2), or 8 mg /24 h (40 cm^2) of Rotigotine. Application of study medication started at the Baseline Visit. Rotigotine was administered once daily starting at 4 mg / 24 h. Doses were then up-titrated in weekly increments of 2 mg / 24 h until optimal or maximum dose (16 mg / 24 h) was reached and the Maintenance Period could be started. The duration of the Titration Period varied from 1 to 7 weeks ± 3 days. The Maintenance Period lasted 12 weeks ± 5 days. Thereafter, during the De-Escalation Period, the dose of study medication was decreased by 2 mg / 24 h every other day. The De-Escalation Period might have lasted up to 12 days.

Serious adverse events	Placebo	Rotigotine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	2 / 35 (5.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 33 (3.03%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 33 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 33 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Rotigotine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 33 (51.52%)	20 / 35 (57.14%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 33 (6.06%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 33 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	2 / 33 (6.06%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Hyperkinesia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	4 / 33 (12.12%)	6 / 35 (17.14%)	
occurrences (all)	11	7	
Dizziness			

subjects affected / exposed	3 / 33 (9.09%)	3 / 35 (8.57%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 33 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	1 / 33 (3.03%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 33 (6.06%)	8 / 35 (22.86%)	
occurrences (all)	3	11	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 33 (6.06%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 33 (3.03%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	0 / 33 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2013	- The study design was changed to a hypothesis-generating pilot study - The number of subjects was reduced. Subject enrollment had to continue until approximately 64 subjects were randomized or until the end of Jul 2013 (whichever occurred first) - The study location was changed from being conducted globally to being conducted in only Europe and the USA - Additionally some administrative information was updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported